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MR assessment of fetal lung development using lung volumes and signal intensities

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Abstract The purpose of this study was to evaluate the monitoring and diagnostic potential of MRI in fetal lung development and disease using lung volume and signal intensity changes through gestation. Thirty-five healthy fetuses (22–42 weeks) were examined on a 1.5-T MR system using sagittal T2w single-shot fast spin-echo imaging (TR indefinite, TE 90 ms, slice thickness/gap 3–5/0 mm, FOV 26–40 cm, NEX 0.5). Fetal body and lung were segmented manually and volumes calculated. Signal intensities (SI) of fetal lung and three reference values were measured on the section best displaying the lung. Regions of interests were defined by including the maximal organ area possible. The following SI ratios were generated: lung/liver, lung/amniotic fluid, lung/muscle, liver/fluid and liver/muscle. Volumes and ratios were correlated with gestational age. Data from seven fetuses with pulmonary pathology were compared with these normative values. Absolute lung volume varied from 12.3 to 143.5 cm³

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Keywords MRI · Fetal lung · SSFSE · Pulmonary hypoplasia · Signal intensity

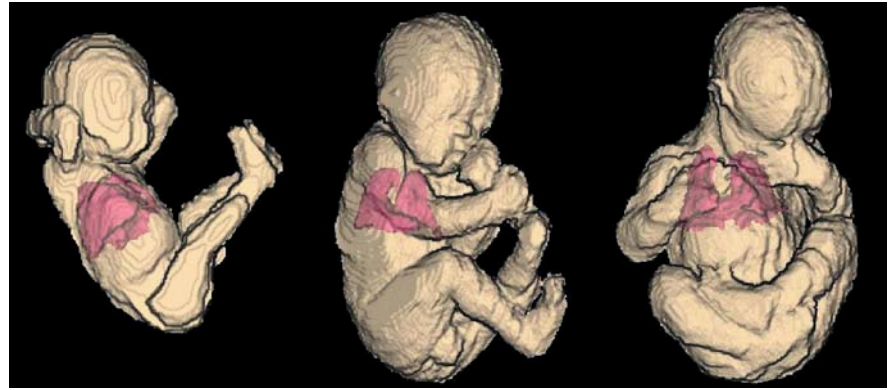
Introduction

As a critical determinant of post-natal survival, fetal lung growth and maturity are a key parameter in prenatal diagnostics, both for risk assessment in preterm birth and for predicting outcome in fetal disorders associated with pulmonary hypoplasia. Diagnosis of lung maturity currently relies on surfactant-related lipid levels in amniotic

fluid withdrawn by amniocentesis [1, 2]. Non-invasive imaging is clearly preferable. Ultrasound reveals the vast majority of clinically significant fetal anomalies [3]. However, accurate prediction of lung development and maturity with ultrasound is difficult, even in experienced hands.

The introduction of ultrafast sequences has rapidly expanded the indications for fetal magnetic resonance

Fig. 1 3D MR reconstructions of T2-weighted SSFSE sequences (TR indefinite/TE 90 ms, slice thickness/gap 3–4/0 mm, FOV 32 cm, matrix 256×256) of fetal body and lung in uncomplicated pregnancies at different weeks of gestation (*left* 26; *middle* 34; *right* 36)



imaging (MRI) [4–10]. MRI is a valuable adjunct to ultrasound in the prenatal diagnosis of fetal chest masses [11–14]. Several groups have investigated fetal lung volume as a predictor of hypoplasia using echo-planar imaging [15, 16] or fast T2-weighted imaging [12, 17, 18]. More recently, using a single-shot fast spin-echo (SSFSE) sequence, Ikeda et al. focused on signal intensity (SI), showing that the abnormal density of hypoplastic lung in one fetus generated a marked difference in SI from its twin [19]. Kuwashima et al. confirmed this finding using half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences: after 26 weeks of gestation, low-intensity fetal lung on MRI indicated pulmonary hypoplasia [20].

The aim of our own study was to further investigate the potential of MRI in fetal pathophysiology and prenatal diagnostics of normal lung growth as well as assessment of lung maturity by combining the two parameters of fetal lung volume and SI measurement.

Materials and methods

Patient population and study design. Between January 2000 and October 2001, 35 pregnant women, aged 29.4 ± 5.1 years (mean value \pm standard deviation, range: 19–39) and gestational age 31.6 ± 6.5 weeks (22–42) were recruited either at routine prenatal ultrasound at weeks 18–22 of gestation in the obstetric clinic or following clinically indicated MR pelvimetry performed in the 3rd trimester in our department. All had uncomplicated singleton pregnancies. Fetal malformation and growth retardation were excluded by prenatal ultrasound, performed in all cases by an experienced investigator with a 4-MHz sector probe (128×P/10, Acuson, Mountain View, CA) or multifrequency probe (3.5–5.1 MHz; Siemens Elegra, Issaquah, WA). The study protocol had been approved by our institutional review board, and written informed consent was provided by all participating women.

MRI. Fetal MRI was performed on a 1.5 T system (Signa Horizon LX and CV/i, General Electric Medical Systems, Milwaukee, WI). A sagittal localizing two-dimensional (2D) fast spoiled gradient-echo (FSPGR) sequence was performed (TR 150 ms, TE 1.4 ms, flip angle 60°, bandwidth 31.25 kHz, slice thickness/gap 7–10/0–3 mm, FOV 32–36 cm, matrix 256×160, NEX 1) using the body coil, followed by T2-weighted SSFSE MRI (TR indefinite, TE 90 ms, bandwidth 31.25 kHz, slice thickness/gap 3–5/0 mm,

FOV 26–40 cm, matrix 256×256, NEX 0.5) sagittal to the fetus encompassing the entire fetal body. The body coil was used in the 16 cases in which fetal MRI was performed after clinically indicated MR pelvimetry; a torso phased-array coil to optimize signal-to-noise ratio was used in the remaining cases. Using maternal breath-hold SSFSE MRI, each individual image was acquired separately with an acquisition time of 0.8 s and a 6-s interimage interval to avoid saturation effects, resulting in a total imaging time of about 5 min. No subject was premedicated.

Fetal lung SI and three reference SI values—fetal liver, amniotic and/or fetal gastric fluid and maternal muscle—were measured using an Advantage Workstation 3.1 (GE Medical Systems, 283 rue de la Minière, B.P. 34 78533 Buc Cedex, France) on the same section to avoid signal variation because of different section spin saturations and to minimize nearfield artifacts of the surface coil (measurement on the same section was considered to be as equidistant from the surface coil as possible). The following SI ratios were generated: lung/liver, lung/fluid, lung/muscle, liver/fluid and liver/muscle. The section best displaying the lung without amniotic fluid motion artifacts was chosen. A region of interest (ROI) was then defined by including the maximal organ area possible, omitting the border zones to avoid partial volume effects and, in particular with the fetal lung, omitting the blood vessels. SI values were measured on one section per lung per fetus and the means taken for statistical analysis.

Fetal body, lung and liver volumes were calculated on either a high-end workstation (Unix; Silicon Graphics, Mountain View, CA) running segmentation and 3D modeling software (ProVision Version 3.0b; Algotec, Raanana, Israel) as previously described by our group [7] or an Advantage Workstation 3.1 with an integrated 3D reconstruction tool. The same investigator (TK) manually segmented the fetal body, lung and liver on each section in all fetuses. The post-processing software then created a 3D surface model and automatically calculated the volume of each 3D reconstruction (Fig. 1). Lung volumes were calculated relative to total body and liver volumes (%).

Statistical analysis. All analyses were performed in StatView 5.0.1 (SAS Institute, Inc., Campus Drive, Cary, NC, 27511). Continuous variables were presented as means and standard deviations. Spearman's rank correlation was used to analyze the development of SI ratio and relative lung volume with gestational age. Bonferroni's correction was used to address the problem of multiple comparisons. Since five SI ratios were analyzed, a corresponding P -value < 0.01 was considered statistically significant. Similarly, relations of relative lung volume are considered statistically significant for $P < 0.025$.

Pulmonary diagnostics. For comparison with these normative data, and following institutional review board approval, we included retrospectively all the fetuses with known pulmonary

pathology and MR data sets examined at our institute and logged in our relational database (Oracle version 8: Oracle, Redwood Shores, CA, 94065). Out of 60 examinations for this indication, seven fetuses with pulmonary pathology could be identified aged 27.0 ± 5.5 (22–36) weeks of mothers aged 31.3 ± 6.4 (25–42) years. The same SSFSE sequence as described above was used. Volumes (in lung sequestrum and CCAM including only healthy lung, in hydrops fetalis including only lung without pleural effusions and in diaphragmatic hernias including only residual lung) and SI measures (in lung sequestrum, CCAM and diaphragmatic hernias including only healthy lung) were performed as described above. A multiple linear regression was used to compare age-adjusted values of volumes and SI between normal and pathological fetuses.

Results

Fetal structure and amniotic fluid SI measurement were feasible in all cases. In four cases, maternal muscle SI could only be measured on one side; in another case, in the 3rd trimester, it could not be measured at all, since the muscle was outside the FOV, so that the corresponding ratios were unobtainable. 3D reconstruction and volumetry of fetal body, lung and liver from the MR data sets acquired with the T2-weighted SSFSE sequences were feasible in all cases.

Mean sizes of the regions of interests were for the lung 615 mm^2 (144–1,567 mm^2), for the liver 706 mm^2 (72–2,028 mm^2), for the fluid 687 mm^2 (32–2,932 mm^2) and for the maternal muscle 549 mm^2 (101–1,103 mm^2). Mean SI ratios were lung/liver 2.68 ± 0.76 (1.60–4.43), lung/fluid 0.66 ± 0.13 (0.47–1.05), lung/muscle 5.13 ± 1.28 (2.54–7.72), liver/fluid 0.26 ± 0.07 (0.16–0.45) and liver/muscle 2.08 ± 0.84 (1.00–4.02). Lung/fluid and lung/muscle ratios did not correlate with gestational age ($P=0.36$ and $P=0.016$, respectively). The lung/liver ratio increased, and liver/fluid and liver/muscle ratios decreased with gestational age ($P<0.001$ in all cases).

Lung volume ranged from 12.3 to 143.5 cm^3 , liver volume from 17.0 to 211.0 cm^3 and fetal body volume from 354 to $3,750 \text{ cm}^3$, all increasing with gestational age ($P<0.001$). Relative lung/total body volume ranged from 1.6 to 5.0% , liver/total body volume from 4.3 to 7.7% and lung/liver volume from 29.7 to 100.0% . Relative lung volumes decreased with gestational age (total body: $P=0.001$ (Fig. 2); liver: $P=0.001$).

Pathologies in the seven abnormal fetuses were hydrothorax, CCAM and diaphragmatic hernia ($n=2$ each) and lung sequestrum ($n=1$) (Table 1). Lung volume ranged from 2.1 to 20.6 cm^3 . Relative lung/total body volume ranged from 0.2 to 1.4% . Absolute and relative lung volumes were lower than in the age-adjusted normal population ($P<0.001$) (Fig. 2). The following SI ratios did not differ significantly from those in the normal population: lung/liver ($P=0.09$), lung/fluid ($P=0.38$) and liver/fluid ($P=0.21$); lung/muscle ($P<0.001$) and liver/muscle ($P=0.002$) ratios were higher. Pregnancy was terminated in the two cases of hydrops fetalis,

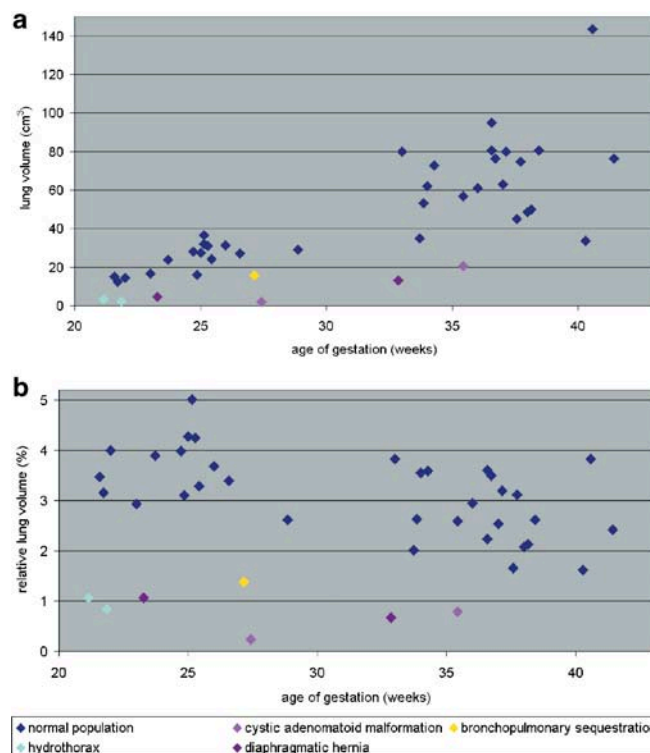


Fig. 2 Correlation between fetal lung volume and gestational age in normal fetuses and fetuses with pulmonary malformation. **a** Absolute lung volume increases with gestational age, while **b** lung volume relative to total body volume decreases, probably due to an increase in subcutaneous fat towards term. Absolute and relative lung volumes were smaller in malformed than in normal fetuses

Table 1 Clinical and MRI features in the fetuses with pulmonary malformation

Case	Gestational age at MRI (weeks)	Diagnosis	Relative fetal lung volume (% total body volume)
1	22	Hydrops fetalis, hydrothorax	0.84
2	22	Hydrops fetalis, hydrothorax	0.87
3	24	Diaphragmatic hernia	1.06
4	28	CCAM	0.23
5	28	Lung sequestrum	1.39
6	33	Diaphragmatic hernia	0.67
7	36	CCAM	0.78

autopsy revealing arthrogryposis multiplex congenita in one case, and no conclusive diagnosis in the other (Fig. 3). In the case with a lung sequestrum (Fig. 4), the coexistent pleural effusion was aspirated and a thoracoamniotic shunt inserted during pregnancy, but the infant died in the neonatal period. In the first CCAM case (Fig. 5) the cyst was serially aspirated in pregnancy and a thoracoamniotic shunt inserted, but death from respira-

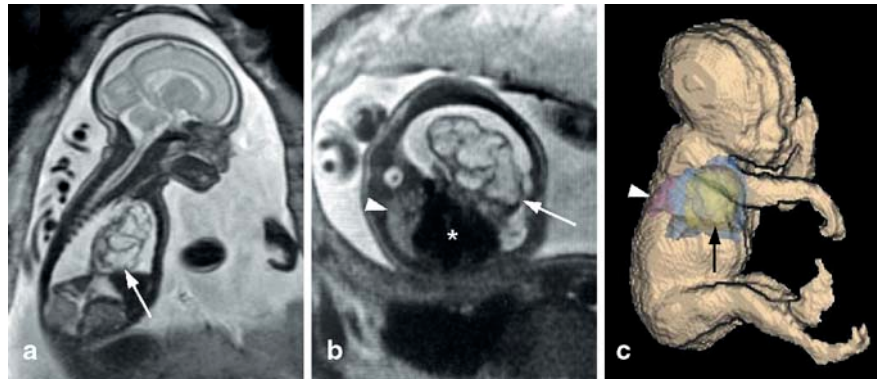


Fig. 3 Twenty-eight-week fetus with left lung CCAM. **a** Sagittal and **b** axial T2-weighted SSFSE sequences (TR indefinite/TE 90 ms, slice thickness/gap 3–4/0 mm, FOV 32 cm, matrix 256×256), **c** 3D surface model. The CCAM (arrows) is displacing the mediastinum and heart (asterisk) to the right, thus compressing

the right lung (arrowhead), resulting in a relative volume of only 0.2% (absolute volume, 2.1 cm³). Despite serial CCAM aspiration in pregnancy, death from respiratory failure occurred post-partum at 33 weeks of gestation

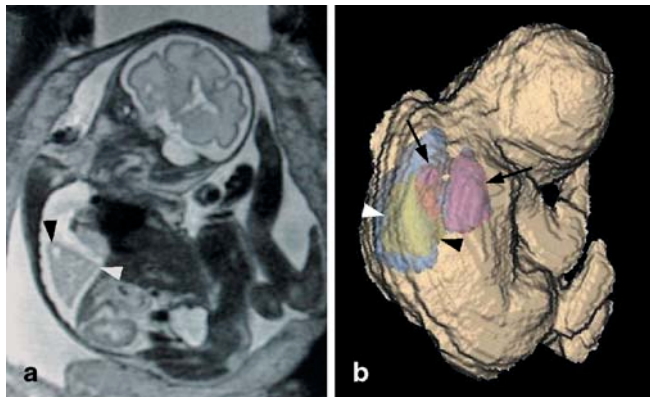


Fig. 4 Twenty-eight-week fetus with left lung sequestrum. **a** Coronal T2-weighted SSFSE image (TR indefinite/TE 90 ms, slice thickness/gap 3–4/0 mm, FOV 32 cm, matrix 256×256). **b** 3D reconstruction. Arrowheads: pleural effusion and lung sequestrum (volume, 16.6 cm³). Arrows: normal right lung and rest of left lung (combined volume, 15.8 cm³; relative lung volume, 1.4%)

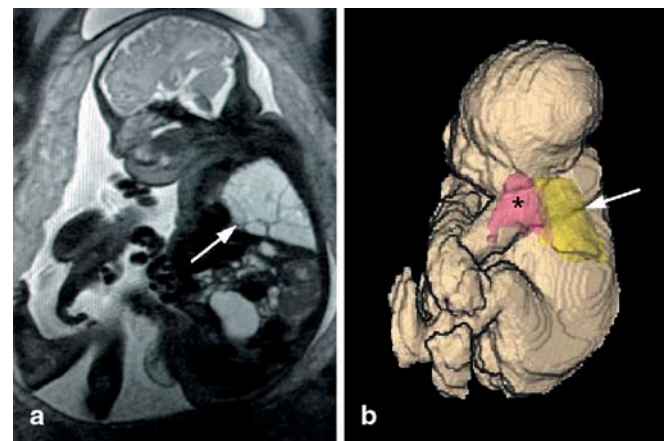


Fig. 5 Thirty-six-week fetus with CCAM. **a** Sagittal T2-weighted SSFSE image (TR indefinite/TE 90 ms, slice thickness/gap 3–4/0 mm, FOV 32 cm, matrix 256×256) showing CCAM (arrows) occupying left hemithorax. **b** 3D reconstruction of right lung (asterisk), relative volume 0.8% (arrow, CCAM)

tory failure occurred in the post-partum period, as in the second CCAM case (Fig. 6). In one case with a diaphragmatic hernia scanned at 24 weeks, GA surgical closure of the diaphragmatic defect was performed post-partum; however, the fetus died a few weeks later of pulmonary hypertension. The second case of a diaphragmatic hernia was associated with a cerebral malformation (Dandy Walker syndrome); the fetus died in the neonatal period.

Discussion

As expected, absolute fetal lung volume increased with gestational age in the normal population, confirming pre-

vious MRI studies [16, 17, 19]. However, fetal volumetry used as we have previously described [7] showed a decrease in relative lung volume towards term, probably because of an increase in subcutaneous fat.

In contrast to earlier studies, fetal lung SI did not change significantly with gestational age. However, direct comparison is difficult if the differences in imaging strategies and/or study populations are not considered [15, 19, 20]. We found a highly significant change with gestational age in the lung/liver SI ratio, but not in the lung/fluid or lung/muscle ratios. It is true that using T2*-weighted echo-planar sequences, Duncan et al. (1997) also found a change in fetal liver SI with gestational age, and suggested this might be due to a change in liver iron concentration following a progressive decrease in

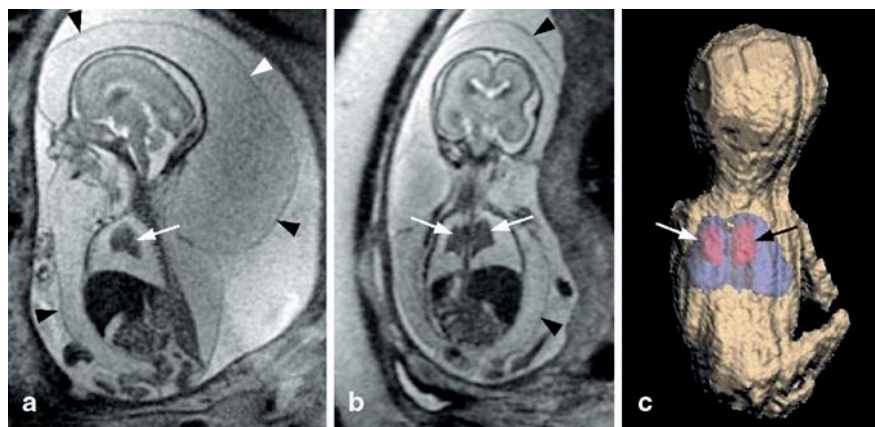


Fig. 6 Twenty-two-week fetus with hydrops fetalis. **a** Sagittal and **b** coronal T2-weighted SSFSE images (TR indefinite/TE 90 ms, slice thickness/gap 3–4/0 mm, FOV 32 cm, matrix 256×256) showing massive subcutaneous edema (arrowheads) and marked pleural effusions with secondary pulmonary compression (ar-

rows). **c** 3D surface model showing lung (arrows), volume 2.3 cm³ and relative volume of 0.9% (body volume was calculated by excluding the subcutaneous edema). Autopsy at 24 weeks confirmed hydrops fetalis with subcutaneous edema and pleural effusions, with no concomitant malformations

hepatic hemoglobin production [21]. As our study also showed significant changes in the liver/fluid and liver/muscle ratios, it is more likely that liver SI changes with gestational age, which tends to invalidate Kuwashima et al.'s interpretation of their results using fetal liver as reference structure. On the evidence provided in the present study, we believe that the liver is not a suitable reference structure.

Our study included a small historical series of fetuses with lung malformations. Ultrasound is the established imaging modality in prenatal screening and malformation diagnostics. However, its ability to assess fetal lung is limited [22]. Recent studies indicate that MRI may be a valuable adjunct, e.g., in identifying the origin of extensive chest tumors [11, 13, 14] or in planning in utero interventions, delivery, and immediate post-natal surgery [23–25].

As expected, lung volumes were smaller in the malformed fetuses than in the normal population, confirming previous reports [17, 26, 27]. As earlier investigators stated [17], setting a relative lung volume threshold for diagnosing pulmonary hypoplasia would require a very high number of subjects. However, in our study the lower limit of normal lung volume was 1.6%, against an upper limit in the hypoplastic group of 1.4%, suggesting that it should prove possible to create a percentile curve based on a large study population to define pulmonary hypoplasia.

We encountered technical challenges in the SI analysis. In contrast to computed tomography, where tissue density can be expressed as an absolute value in Hounsfield units, SI measures in MRI require comparison with a reference structure. The ideal structure is one with imaging properties that remain unchanged during pregnancy, in the vicinity of the fetal lung to avoid SI loss because of a difference in distance from the phased-array

coil. Conventional reference structures include fetal liver and amniotic fluid [20, 21]. For the reasons already stated, we believe that the liver is unsuitable for this purpose, and we thus introduced maternal iliac muscle/rectus abdominis as an additional reference structure.

Next to the technical challenges discussed above, there are some other limitations to our study, one being the small size of our normal fetus population. Furthermore, 3D reconstruction took several hours per fetus, limiting not only the sample size as mentioned above, but also the clinical feasibility of the method. Another limitation is the relative rarity of pulmonary malformations, detected in only seven fetuses out of the total of 60 MRI scans performed for suspected fetal malformation. Clinical outcome in these cases with pulmonary hypoplasia was poor: termination in two cases, and death from respiratory failure in the remainder.

In conclusion, in accordance with previous studies [16, 17, 19], we believe that normative MRI data for fetal lung volume may have important clinical applications in confirming and quantifying fetal pulmonary hypoplasia, a relatively rare but potentially lethal malformation. MRI is likely to gain an increasing role as a complementary imaging method in diagnosing fetal lung abnormalities and planning fetal and post-natal surgery. In contrast to earlier studies [15, 19, 20], our study found no place for SI measurement in assessing fetal lung development.

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